PDL DRUG REVIEW

Proprietary Name: Priftin®
Common Name: rifapentine
PDL Category: Antimycobacterials - Antituberculosis

Comparable Products	Preferred Drug List Status
Rifampin	Preferred

Summary

Pharmacology/Usage: Rifapentine, the active ingredient of Priftin®, is an antimycobacterial agent. Rifapentine, a cyclopentyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis*; however, it does not affect mammalian cells at levels that are active against these bacteria. It forms a stable complex with bacterial DNA-dependent RNA polymerase, leading to repression of RNA synthesis and cell death.

Rifapentine resistance seems to be associated with monotherapy; therefore, rifapentine should always be used in combination with other antituberculosis drugs.

Indication: For adults and children ≥12 years for the treatment of active pulmonary tuberculosis (TB) caused by *Mycobacterium tuberculosis*. Priftin® must always be used in combination with ≥1 antituberculosis (anti-TB) drugs to which the isolate is susceptible. *Limitations of use*: Do not use Priftin® monotherapy in either the initial or the continuation phases of antituberculous treatment; Priftin® should not be used once-weekly in the continuation phase regimen in combination with isoniazid (INH) in HIV-infected patients with active pulmonary TB because of a higher rate of failure and/or relapse with rifampin (RIF)-resistant organisms; Priftin® has not been studied as part of the initial phase treatment regimen in HIV-infected patients with active pulmonary TB.

For adults and children ≥2 years for the treatment of latent tuberculosis infection caused by *Mycobacterium tuberculosis* in patients at high risk of progression to tuberculosis disease (including those in close contact with active TB patients, recent conversion to a positive tuberculin skin test, HIV-infected patients, or those with pulmonary fibrosis on radiograph). *Limitations of use:* Active tuberculosis disease should be ruled out before initiating treatment for latent tuberculosis infection; Priftin® must always be used in combination with isoniazid as a 12-week once-weekly regimen for the treatment of latent tuberculosis infection; Priftin® in combination with isoniazid is not recommended for individuals presumed to be exposed to rifamycin or isoniazid resistant *M. tuberculosis*.

This is a pregnancy category C medication.

Dosage Forms: Film-coated Tablets: 150mg

Recommended Dosage: Take Priftin® with food. In addition, the tablets may be crushed and added to a small amount of semi-solid food for patients that cannot swallow tablets. *Active Pulmonary TB*: Priftin® is only

recommended as part of regimens consisting of a 2 month initial phase followed by a 4 month continuation phase; it should not be used in the treatment of active pulmonary tuberculosis caused by rifampin-resistant strains. For the initial phase, take Priftin® 600mg BID for 2 months as directly observed therapy (DOT), with an interval of no less than 3 consecutive days between doses, in combination with other anti-tuberculosis drugs as part of an appropriate regimen that includes companion drugs such as isoniazid (INH), ethambutol (EMB), and pyrazinamide (PZA). For the continuation phase that follows the initial phase, treatment includes Priftin® 600mg QW for 4 months in combination with isoniazid or another appropriate antituberculosis agent for susceptible organisms administered as DOT. *Latent TB infection:* Take Priftin® QW in combination with isoniazid for 12 weeks as DOT. The recommended dose is based on weight, up to a maximum of 900mg QW. Please refer to the table below for the weight-based dose of Priftin®, which was adapted from the prescribing information.

Weight Range	Priftin dose	Number of Priftin tablets
10-14kg	300mg	2
14.1-25kg	450mg	3
25.1-32kg	600mg	4
32.1-50kg	750mg	5
>50kg	900mg	6

The pharmacokinetics of rifapentine has not been studied in renally impaired patients. In studies with patients with hepatic impairment, the pharmacokinetics was similar between patients with and without hepatic impairment.

Liver transaminases elevations may occur in patients receiving Priftin®. It is recommended to monitor for symptoms of liver injury while taking Priftin®. It is also recommended that patients with abnormal liver tests and/or liver disease or patients starting treatment for active pulmonary TB should only be given Priftin when it is of necessity and under strict medical supervision. In these patients, it is recommended to obtain serum transaminase levels before starting treatment and then every 2-4 weeks while on treatment.

Drug Interactions: Rifapentine is an inducer of CYP450 enzymes, including CYP3A4 and CYP2C8/9. Thus, Priftin® may increase the metabolism of drug that are metabolized by these enzymes if given concomitantly. Drug interactions with Priftin® may require dose adjustments with the following: antiarrhythmics, antibiotics, oral anticoagulants, anticonvulsants (e.g. phenytoin), antimalarials, azole antifungals, antipsychotics (e.g. haloperidol), barbiturates, benzodiazepines (e.g. diazepam), beta-blockers, CCBs, cardiac glycoside preparations, corticosteroids, fibrates, oral hypoglycemics (e.g. sulfonylureas), hormonal contraceptives/progestins, immunosuppressants, methylxanthines, narcotic analgesics, PDE-5 inhibitors, thyroid preparations, and TCAs. It is recommended that patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control, as Priftin® may reduce the effectiveness of hormonal contraceptives. Concomitant use with protease inhibitors (PIs) and certain reverse transcriptase inhibitors (RTIs) may cause a significant decrease in plasma levels and loss of therapeutic effect of the PIs or RTIs.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Priftin® combination) minus reported % incidence for rifampin combination in clinical trials during the initial phase. Please note that an incidence of 0% means the incidence of the active drug was the same as or less than placebo.* The most frequently reported adverse events included anemia (0%), lymphopenia (0.3%), neutropenia (0.3%), leukocytosis (0%), thrombocytosis (1.9%), thrombocytopenia (0%), lymphadenopathy (0.5%), nonprotein nitrogen increased (0.3%), conjunctivitis (1.6%), dyspepsia (0%), vomiting (0%), nausea (1.1%), diarrhea (0.8%), back pain (1.2%), abdominal pain (0%), fever (0%), anorexia (0%), ALT increased (0%), AST increased (0%), arthralgia (0%), headache (0%), dizziness (0%), hemoptysis (2%), coughing (3.6%), rash (0%), sweating increased (0.3%), pruritus (0%), and macro papular rash (0.9%).

Priftin® may cause a red-orange discoloration of body tissues and/or fluids (e.g. skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid). Furthermore, contact lenses or dentures may become permanently stained.

Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterials, including Priftin®, ranging from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, it is recommended to discontinue antibacterial use not directed against *C. difficile* if possible.

Priftin® should be avoided in patients with porphyria.

Contraindications: History of hypersensitivity to rifamycins

Manufacturer: Sanofi-Aventis

Analysis: There were two randomized, open-label controlled studies performed to assess the safety and efficacy of Priftin® for the treatment of active pulmonary tuberculosis. Study 1 was an active-controlled trial that included HIV-negative patients who were randomized to Priftin® or rifampin, both taken in combination with isoniazid/pyrazinamide/ethambutol during the initial 2 month phase; during the 4 month continuation phase, patients continued on with Priftin® and isoniazid or rifampin and isoniazid, but at modified doses. The table below contains results of sputum conversion.

	Priftin® regimen	rifampin regimen
Status at end of 6 months of treatment		
Converted	87% (N=248/286)	80% (N=226/283)
Not Converted	1% (N=4/286)	3% (N=8/283)
Lost to Follow-up	12% (N=34/286)	17% (N=49/283)
Status through 24 month follow-up		
Relapsed	12% (N=29/248)	7% (N=15/226)
Sputum Negative	57% (N=142/248)	64% (N=145/226)
Lost to follow-up	31% (N=77/248)	29% (N=66/226)

Note that the risk of relapse was greater in the Priftin® regimen. Higher relapse rates were associated with a lower rate of compliance and a failure to convert sputum cultures at the end of the initial 2 month treatment phase. In addition, there were 22 deaths during the study, 11 in each treatment group.

The second study included HIV-negative and positive patients (N=1075). Patients with culture-positive, drug-susceptible pulmonary tuberculosis who completed the initial 2-month phase of treatment with a rifampin regimen were then randomized to receive Priftin® and isoniazid QW or rifampin and isoniazid twice weekly for the 4 month continuation phase. The table below contains results of the sputum conversion at the end of treatment.

	Priftin® regimen	rifampin regimen
Status at end of 4 months continuation phase		
Treatment response	93.8% (N=471/502)	91% (N=457/502)
Not converted	1% (N=5/502)	1.2% (N=6/502)
Did not complete treatment	4.2% (N=21/502)	7% (N=35/502)
Deaths	1% (N=5/502)	0.8% (N=4/502)
Status through 24 month follow-up		
Relapsed	8.7% (N=41/471)	4.8% (N=22/457)
Sputum Negative	79.4% (N=374/471)	80.1% (N=366/457)
Lost to follow-up	7.9% (37/471)	9.8% (N=45/457)
Deaths	4% (N=19/471)	5.3% (N=24/457)

In HIV-negative patients, higher relapse rates were seen in patients with a positive sputum culture at 2 months, cavitation on chest x-ray, and bilateral pulmonary involvement. There were 61 HIV-positive patients who were

assessed for relapse. The rates of relapse were 16.7% in the Priftin® group as compared with 9.7% in the rifampin group. The death rate was not different between treatment regimens.

One randomized, open-label, active-controlled study assessed the safety and efficacy of 12 weekly doses of Priftin® in combination with isoniazid administered by DOT as compared to 9 months of self-administered daily isoniazid. The outcome assessed was the development of active tuberculosis disease, defined as culture confirmed tuberculosis in adults and culture-confirmed or clinical tuberculosis in children <18 years of age, at 33 months after enrollment. Results can be found in the table below.

Outcome	Priftin® regimen (N=3074)	isoniazid (N=3074)	Difference
Active Tuberculosis	5 (0.16%)	10 (0.32%)	-0.16
Cumulative TB rate	0.17%	0.35%	-0.17
Deaths	22 (0.72%)	35 (1.14%)	-0.42
Lost to follow-up	320 (10.41)	357 (11.61)	-1.20

81.2% of the Priftin® regimen group completed treatment as compared with 68.3% in the isoniazid group. In a pediatric subgroup analysis (N=742) that included data from the main study and the extension suggested that there was 1 child in the isoniazid group developed tuberculosis as compared with none in the Priftin® regimen group. In the HIV subgroup analysis (N=399) that included data from the main study and the extension suggested that there were 2 patients (out of 206) who developed tuberculosis in the Priftin® regimen group as compared with 6 patients (out of 193) in the isoniazid group.

Place in Therapy: While rifampin is generally used as first-line therapy for the treatment of mycobacterial infections, including tuberculosis, rifapentine (Priftin®) was found to be safe and as effective as compared to rifampin in clinical trials that included patients with active tuberculosis. However, Priftin® should not be used for active pulmonary TB in patients with HIV infection, children <12 years of age, or for patients with culture-negative or extrapulmonary tuberculosis.[2] In addition, Priftin®, in combination with isoniazid, is FDA approved for adults and children ≥2 years for the treatment of latent TB infection caused by *Mycobacterium tuberculosis* in patients at high risk of progression to tuberculosis disease. Drug interaction and hepatotoxicity are warnings with use.

Priftin is considered a safe and effective alternative to rifampin and allows less frequent (weekly) dosing in certain circumstances which is of use especially in directly observed therapy. It is recommended Priftin be added as a preferred agent.

PDL Placement: ☒ **Preferred**
☐ **Non-Preferred**

References

[1] Priftin [package insert]. Bridgewater, NJ: Sanofi-Aventis US; 2014.
[2] UpToDate desktop version. Rifamycins (rifampin, rifabutin, rifapentine). Accessed January 2016.